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(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017-5755 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)* : BRIGHTY, Katherine, E. [US/US]; 24 Courtland Drive, Groton, New London County, CT 06340 (US).

(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017-5755 (US).

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(54) Title: AZABICYCLO QUINOLONE CARBOXYLIC ACIDS

(57) Abstract

Quinolone carboxylic acids 7-substituted by azabicyclo groups have antibacterial activity.

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AZABICYCLO QUINOLONE CARBOXYLIC ACIDS

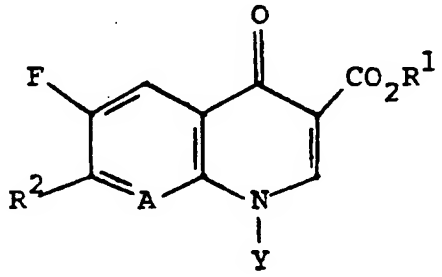
Background of the Invention

The invention relates to novel 7-azabicyclo-substituted quinolone carboxylic acids, pharmaceutical compositions containing such compounds and methods of treatment with such compounds.

U.S. Patent 4,571,396 discloses diazabicyclo-substituted naphthyridine-, quinoline- and benzoxazine-carboxylic acids having antibacterial activity. European Patent Publication No. 215650 discloses similar antibacterial diazabicyclo-substituted compounds.

Summary of the Invention

The invention provides antibacterial compounds having the formula



...I

or a pharmaceutically acceptable acid addition salt thereof, wherein

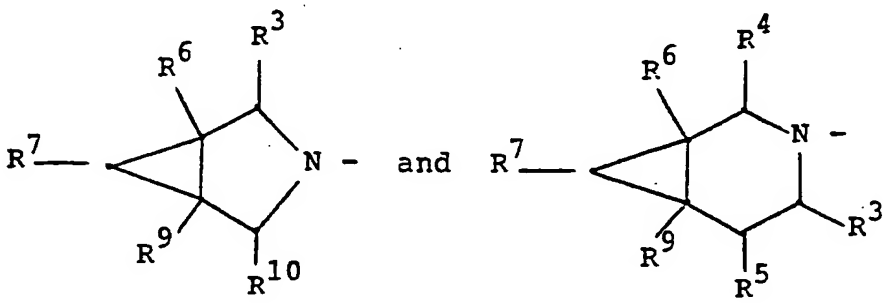
R^1 is hydrogen, a pharmaceutically acceptable cation, or (C_1-C_6) alkyl;

Y, when taken independently, is ethyl, t-butyl, vinyl, cyclopropyl, 2-fluoroethyl, p-fluorophenyl, or o,p-difluorophenyl;

A is CH, CF, CCl, $COCH_3$, C-CH_3, C-CN or N; or

A is carbon and is taken together with Y and the carbon and nitrogen to which A and Y are attached to form a five or six membered ring which may contain oxygen or a double bond, and which may have attached thereto R^8 which is methyl or methylene; and

R^2 is selected from the group consisting of



wherein R^3, R^4, R^5, R^6, R^7, R^9, and R^{10} are each independently H, CH_3, CH_2NH_2, CH_2NHCH_3 or $CH_2NHC_2H_5$, and R^5, R^6, R^7 and R^9 may also independently be NH_2, $NHCH_3$ or NHC_2H_5, provided that not more than two of R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are other than hydrogen.

Preferred compounds of the invention are those of formula I wherein R^1 is hydrogen or a pharmaceutically acceptable cation such as sodium or potassium.

Other preferred compounds are those of formula I wherein Y is cyclopropyl or o,p-difluorophenyl.

Specific compounds of the invention are 7-(3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinolone-3-carboxylic acid,

7-[(1α,2α,5α)-1-aminomethyl-2-methyl-3-azabicyclo-[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-[(1α,2β,5α)-1-aminomethyl-2-methyl-3-azabicyclo-[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-[(1α,2α,5α)-1-amino-2-methyl-3-azabicyclo-[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-[(1α,2β,5α)-1-amino-2-methyl-3-azabicyclo-[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

10-[(1-amino-3-azabicyclo[3.1.0]hex-3-yl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid,

10-[(1α,5α,6α)-6-aminomethyl-3-azabicyclo-[3.1.0]hex-3-yl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid,

7-[(1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

10-[(1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid,

7-[6-aminomethyl-3-azabicyclo[4.1.0]hept-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-[6-amino-3-azabicyclo-[4.1.0]hept-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

7-[(1α,2α,5α,6α)-6-amino-2-methyl-3-azabicyclo[3.1.0]-hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, and

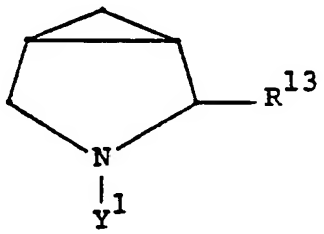
7-[(1α,2α,5β,6α)-6-amino-2-methyl-3-azabicyclo[3.1.0]-hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

The compounds of formula I of the invention wherein R^3, R^4, R^5, R^7 and R^{10} are other than hydrogen can bear these substituents in either of two steric configurations relative to the cyclopropyl group in R^2. The compounds of formula I of the invention include the racemic mixtures and the optical isomers of all of these configurations.

The invention includes a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of the formula I in an antibacterially effective amount.

The invention further includes a method of treating a host, such as an animal or a human being, having a bacterial infection comprising administering to the host an antibacterially effective amount of a compound of the formula I, or a pharmaceutical composition as defined above.

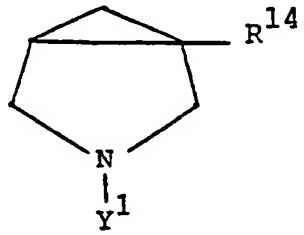
The invention also includes intermediates of use in the preparation of a compound of the formula I. The intermediates have the formulae



wherein Y^1 is hydrogen or benzyl, and R^{13} is methyl, cyano, hydroxymethyl, carboxyl or $CH_2NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl, or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitro-

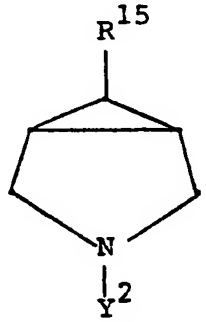
phenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

with the proviso that when Y^1 is hydrogen, then R^{13} is methyl or $CH_2NR^{11}R^{12}$ as defined above; and



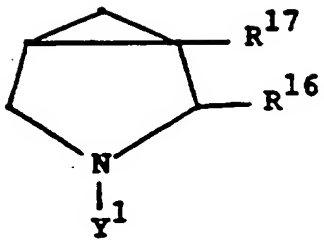
wherein Y^1 is hydrogen or benzyl, and

R^{14} is hydroxymethyl, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$, wherein R^{11} is hydrogen , methyl, or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and



wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl, and

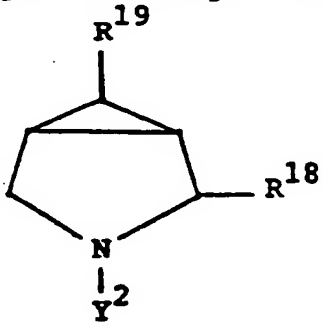
R^{15} is carboxyl, hydroxymethyl, CHO, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$ wherein R^{11} is hydrogen, methyl, or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and



wherein Y^1 is hydrogen or benzyl,

R^{16} is methyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, or $CH_2NR^{11}R^{12}$, and

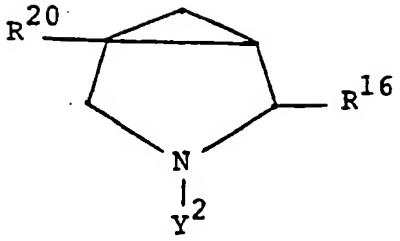
R^{17} is methyl, cyano, carboxyl, hydroxymethyl, or $CH_2NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and



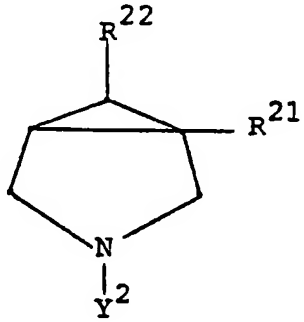
wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,

R^{18} is methyl, cyano, hydroxymethyl, or $CH_2NR^{11}R^{12}$, and

R^{19} is methyl, carboxyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and

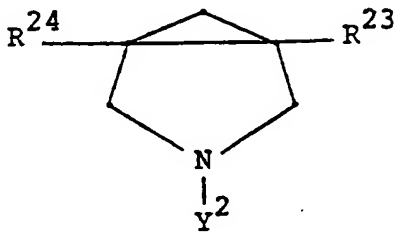


wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,
R^{16} is methyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, or $CH_2NR^{11}R^{12}$, and
R^{20} is methyl, carboxyl, hydroxymethyl, CHO, methoxycarbonyl, ethoxycarbonyl, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$ wherein R^{11} is hydrogen, methyl or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and



wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,
R^{21} is methyl, carboxyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, t-butoxycarbonyl, methoxycarbonyl, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$, and
R^{22} is methyl, carboxyl, hydroxymethyl, CHO, ethoxycarbonyl, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$ wherein R^{11} is hydrogen, methyl or ethyl and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenyl-

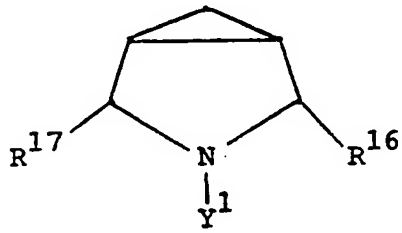
sulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and



wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,

R^{23} is methyl, carboxyl, hydroxymethyl, CHO, methoxycarbonyl, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$, and

R^{24} is methyl, carboxyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl; and



wherein Y^1 is hydrogen or benzyl,

R^{16} is methyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, or $CH_2NR^{11}R^{12}$, and

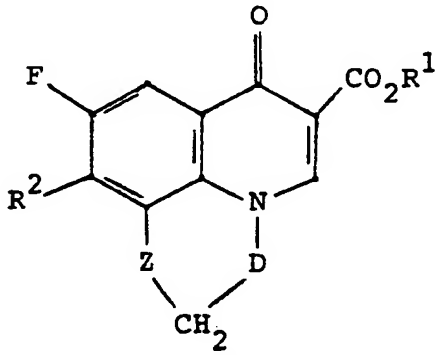
R^{17} is methyl, cyano, carboxyl, hydroxymethyl, CHO, or $CH_2NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl,

vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

Detailed Description of the Invention

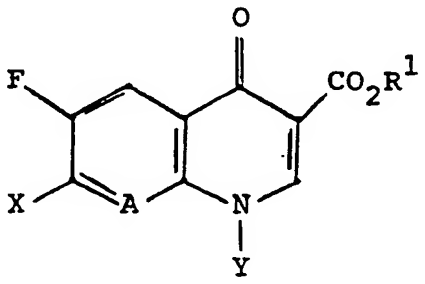
The term "C_1-C_6 alkyl", used in the definition of R^1, denotes saturated monovalent straight or branched aliphatic hydrocarbon radicals having one to six carbon atoms, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc.

When A is carbon and is taken together with Y and the carbon and nitrogen to which A and Y, respectively, are attached to form a five membered ring or a six membered ring, the compounds of formula I in one specific embodiment have the following formula:



wherein Z is CH_2, O or a covalent bond, and D is CH_2, CH=CH, $CHCH_3$ or $C{=}CH_2$.

The compounds (I) of the invention may be prepared by reacting a compound of the formula



...II

with a compound of the formula R^2H wherein R^1, R^2, A

and Y are as defined above in connection with formula I, except that R^2 includes within the definitions of R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} the N-protected groups of NH_2, CH_2NH_2, $NHCH_3$, CH_2NHCH_3, NHC_2H_5, and $CH_2NHC_2H_5$, and X is a leaving group such as fluoro, chloro, bromo or C_1-C_3 alkylsulfonyl. Nitrogen protecting groups are known in the art. Examples of suitable nitrogen protecting groups are C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, 0-nitrophenylsulfonyl, diphenylphosphinyl, p-toluenesulfonyl, and benzyl. The nitrogen protecting group is removed by methods known in the art such as hydrogenation or hydrolysis.

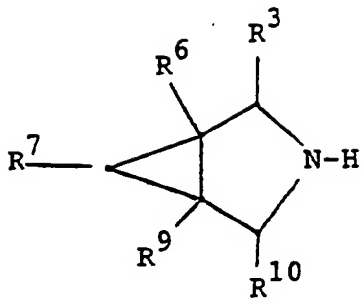
The reaction may be conducted with or without a solvent. The solvent, when used, must be inert under the reaction conditions. Suitable solvents are acetonitrile, tetrahydrofuran, ethanol, chloroform, dimethylsulfoxide, dimethylformamide, pyridine, water, or mixtures thereof.

The reaction temperature usually ranges from about 20°C to about 150°C.

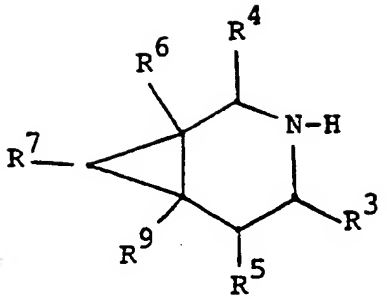
The reaction may advantageously be carried out in the presence of an acid acceptor such as an inorganic or organic base, e.g. an alkali metal or alkaline earth metal carbonate or bicarbonate, or a tertiary amine, e.g. triethylamine, pyridine or picoline.

When R^1 is C_1-C_6 alkyl, conversion to the corresponding acid may be carried out under acidic or basic conditions conventional for hydrolysis of carboxylic acid esters, at about 20° to 150°C.

The starting materials of formula II are known in the art, e.g. as disclosed in U.S. Patents 4,571,396 and 4,775,668. The starting materials of formula R^2H have the following formulae

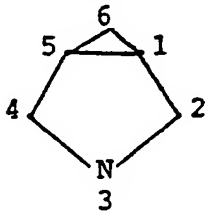


and



III IV

wherein R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are as defined above in connection with a compound of the formula R^2H. Specific examples of such starting materials are the following compounds:



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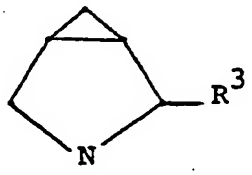

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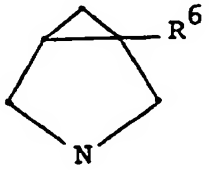

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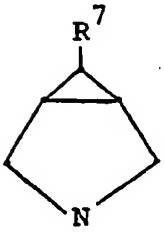

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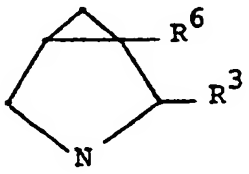

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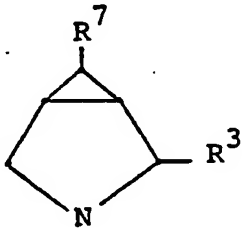

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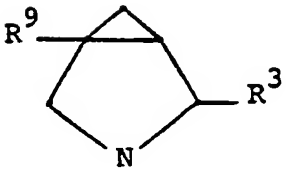

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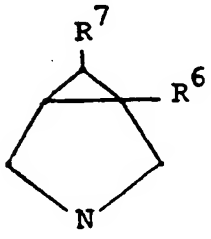

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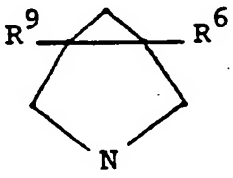

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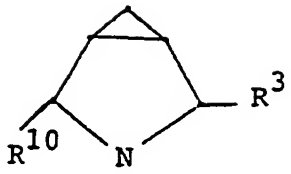

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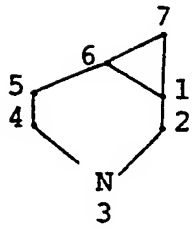

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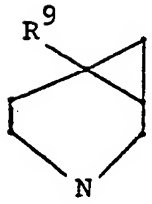

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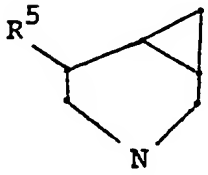

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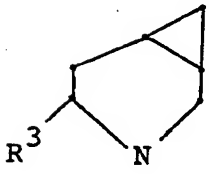

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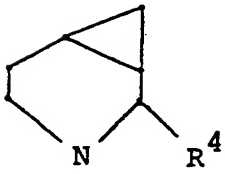

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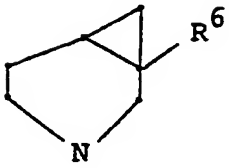

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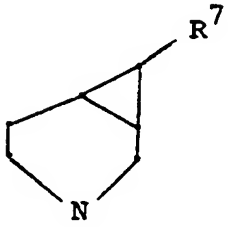

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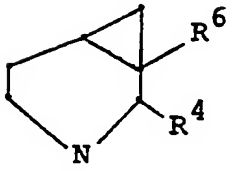

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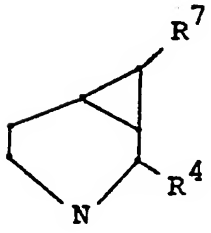

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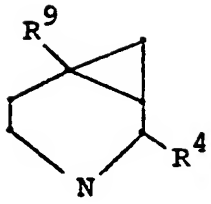

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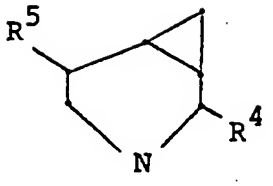

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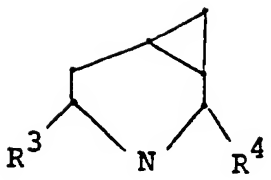

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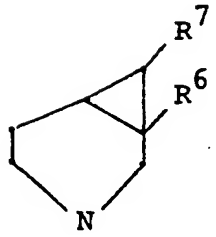

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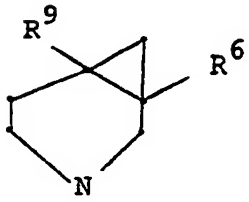

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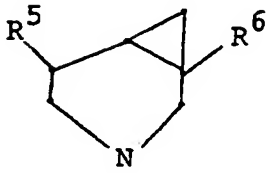

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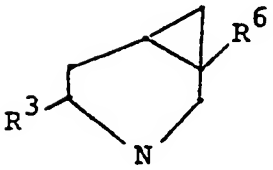

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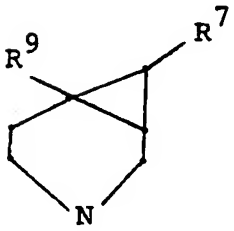

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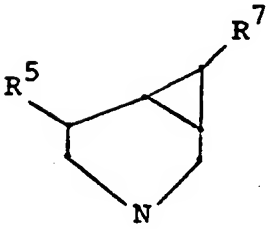

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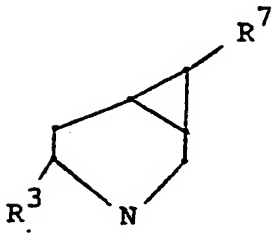

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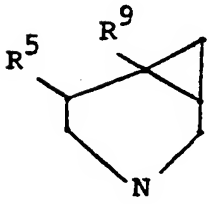

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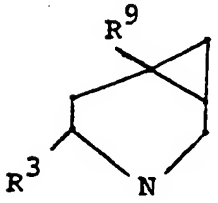

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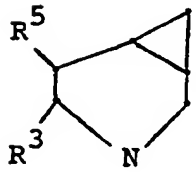


XXXVI

wherein R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are as defined above, except H.

The preparation of the foregoing compounds I to

XXI is discussed below wherein each section is referred to by the formula of the compounds prepared.

3-Azabicyclo[3.1.0]hexane (V)

3-Azabicyclo[3.1.0]hexane may be prepared by the method of D. A. Wood et al. European Patent Publication 0010799 from 1,2-cyclopropanedicarboxylic acid.

2-R^3-Substituted 3-Azabicyclo[3.1.0]hexanes (VI)

2-Cyano-3-azabicyclo[3.1.0]hexane can be prepared by the method of D. A. Wood et al. EP 0010799. Protection of the ring nitrogen, for instance by a benzyl group, then provides 3-benzyl-2-cyano-3-azabicyclo[3.1.0]hexane. Reduction of the nitrile with lithium aluminum hydride gives a compound of the formula VI wherein R^3 is CH_2NH_2 and the 3-N is benzylated. This compound, and all subsequently described amino-substituted azabicyclo[3.1.0]hexyl systems, may be advantageously protected, for instance with an alkoxycarbonyl group such as tert-butoxy-carbonyl, or a carboxylic acid group such as formyl or acetyl, and subsequently debenzylated via hydrogenation to provide the protected 2-aminomethyl-3-azabicyclo-[3.1.0]hexane. After coupling of this debenzylated diamine to a quinolone or naphthyridine nucleus by reaction with a compound of the formula II, the amino-protecting group such as the tert-butoxy-carbonyl or acetyl group can be removed by exposure to acidic conditions.

Alternatively, the diamine 2-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane can be formylated or acetylated by heating to reflux with ethyl formate, according to the procedure of Moffat et al., J. Org. Chem., 27, 4058 (1962), or acetyl chloride. These amides can then be reduced to the corresponding amines with lithium aluminum hydride, to provide a compound of

the formula VI wherein R^3 is CH_2NHCH_3 or $CH_2NHC_2H_5$. This compound may be protected, as in the case of the conversion of the above diamine 2-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane to 2-[(N-acetyl)aminomethyl]- or 2-[(N-tert-butoxycarbonyl)aminomethyl]-3-benzyl-3-azabicyclo[3.1.0]hexane, then debenzylated and appended to the quinolone or naphthyridine nucleus by reaction with a compound of the formula II.

For the case wherein R^3 is CH_3, the above nitrile 3-benzyl-2-cyano-3-azabicyclo[3.1.0]hexane can be hydrolyzed under acidic or basic conditions to the corresponding carboxylic acid, and reduced with lithium aluminum hydride to the alcohol 3-benzyl-2-hydroxymethyl-3-azabicyclo[3.1.0]hexane. Formation of the tosylate followed again by lithium aluminum hydride reduction provides the 2-methyl congener 3-benzyl-2-methyl-3-azabicyclo[3.1.0]hexane, which can be debenzylated as above.

1-R^6-Substituted-3-azabicyclo[3.1.0]hexanes (VII)

These compounds can be prepared from the nitrile 3-benzyl-1-cyano-3-azabicyclo[3.1.0]hexane, whose preparation is reported by Achini and Oppolzer, Tetrahedron Letters, 1975, 369. Alternatively, the nitrile may be synthesized from 3-[(benzyl)(2,3-dihydroxypropyl)amino]propanenitrile via bismesylation, followed by double ring closure with sodium hexamethyldisilazide. Transformation of the nitrile functionality of 3-benzyl-1-cyano-3-azabicyclo-[3.1.0]hexane into CH_3, CH_2NH_2, CH_2NHCH_3 or $CH_2NHC_2H_5$ can be carried out as in section VI above.

Hydrolysis of 3-benzyl-1-cyano-3-azabicyclo-[3.1.0]hexane to 3-benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylic acid can be carried out under basic conditions. Subsequent reaction with

diphenylphosphoryl azide in t-butanol, using the procedure reported by Ninomiya et al., Tetrahedron 1974, 30, 2151, provides the protected amine 3-benzyl-1-tert-butoxycarbonylamino-3-azabicyclo-[3.1.0]hexane. Debenzylation as above yields an amine which can be coupled to the quinolone or naphthyridine nucleus by reaction with a compound of the formula II; acidic removal of the tert-butoxycarbonyl group provides the final product with an amino group as the 1-substituent in the 3-azabicyclo[3.1.0]hexane side chain.

Removal of the tert-butoxycarbonyl group from the protected amine to give 1-amino-3-benzyl-3-azabicyclo-[3.1.0]hexane can be followed by acetylation or formylation and lithium aluminum hydride reduction as above to provide a compound of the formula VII wherein R^6 is $NHCH_3$ or NHC_2H_5. This can be further processed as in Section VI to provide the final product bearing a methylamine or ethylamine at C-1 of the 3-azabicyclo-[3.1.0]hexane side chain.

6-R^7-Substituted-3-azabicyclo[3.1.0]hexanes (VIII)

Addition of ethyl diazoacetate to N-benzyl-maleimide generates a pyrazoline which upon thermolysis provides 3-benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione-6-carboxylic acid ethyl ester. Reduction with lithium aluminum hydride gives 3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane; Swern oxidation followed by oxime formation and lithium aluminum hydride reduction then produces the primary amine, which can be protected or treated as above to give a compound of formula VIII wherein R^7 is CH_2NHCH_3 or $CH_2NHCH_2CH_3$.

Alternatively, 3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane can be treated as in Section VI to provide the 6-methyl derivative. To prepare

compounds with a 6-amino group, hydrogenolytic removal of the benzyl group from 3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane is followed by introduction of a benzyloxycarbonyl group; Jones oxidation at this point provides 3-benzyloxycarbonyl-3-azabicyclo-[3.1.0]hexane-6-carboxylic acid. Curtius rearrangement as in Section VII, using diphenylphosphoryl azide, yields 3-benzyloxycarbonyl-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane, which can be taken on to the analogue bearing a primary amine, or which can be deprotected and further manipulated as in Section VII to provide the compounds of formula VIII wherein R^7 is $NHCH_3$ or NHC_2H_5.

1,2-R^6,R^3-Disubstituted-3-azabicyclo[3.1.0]hexanes (IX)

Modification of the Oppolzer procedure mentioned in Section VII provides this substitution pattern. For the 2-methyl substituted compounds, 3-benzylaminobutanenitrile is used as the starting material. For all other 2-substituents, 3-(benzylamino)-4-[(tetrahydro-2H-pyran-2-yl)oxy]-butanenitrile, available from beta-cyanoalanine via carboxylic acid reduction, alcohol protection and N-benzylation, can be reacted with glycidol to provide 3-[(benzyl)(2,3-dihydroxypropyl)amino]-4-[(tetrahydro-2H-pyran-2-yl)oxy]-butanenitrile. Tosylation of the primary alcohol is followed by base-induced ring closure to 3-[(benzyl)-(2,3-epoxypropyl)amino]-4-[(tetrahydro-2H-pyran-2-yl)oxy]-butanenitrile; sodium hexamethyldisilazide treatment provides 1-benzyl-4-hydroxymethyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-pyrrolidinecarbonitrile. A second tosylation can be followed again by base-induced ring closure to the 3-azabicyclo-[3.1.0]hexane of the formula IX wherein the

2-substituent is tetrahydropyranyloxymethyl, the 1-substituent is cyano, and the 3-aza nitrogen is benzylated. The nitrile functionality of the latter can be transformed into all of the substituents R^6 as in Section VII.

For the elaboration of the C-2 substituent R^3, final C-1 substituents R^6 bearing amino groups can be protected as the corresponding acetamides. Subsequent acid-induced removal of the tetrahydropyran (THP) protecting group gives a primary alcohol which can be transformed into a methyl group as in Section VI. Alternatively, the alcohol can be subjected to a Swern oxidation; reductive amination of the derived aldehyde with ammonium acetate, methylamine or ethylamine then provides the corresponding amines of the formula IX wherein R^6 is CH_3 or amino-protected CH_2NH_2, CH_2NHCH_3, $CH_2NHC_2H_5$, NH_2, $NHCH_3$, or NHC_2H_5, and R^3 is CH_2NH_2, CH_2NHCH_3, or $CH_2NHC_2H_5$. Protection of the resultant 2-amine can be carried out as above, with the tert-butoxycarbonyl protecting group; removal of the benzyl group via hydrogenation provides the free secondary amine, which can be coupled to the quinolone or naphthyridine nucleus, followed by acid-induced removal of the acetamide and tert-butoxycarbonyl groups.

2,6-R^3,R^7-Disubstituted-3-azabicyclo[3.1.0]hexanes (X)

These compounds can be prepared from 3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane; protection as the THP ether, followed by debenzylation, provides 6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-azabicyclo-[3.1.0]hexane. A cyano group can then be introduced into the 2-position by the method of Wood, as in Section VI. Reintroduction of the benzyl group provides 3-benzyl-2-cyano-6-[(tetrahydro-2H-pyran-2-

yl)oxy]methyl-3-azabicyclo[3.1.0]hexane, wherein the two substituents are differentially functionalized. The cyano group can be transformed into the desired 2-substituents, as described in Section VI. At this point, protection of any primary or secondary amine as its acetamide can be followed by acidic removal of the tetrahydropyran protecting group, and elaboration of the primary alcohol into the desired substituent by the methods outlined in Section VIII.

1,4-R^9,R^3 Disubstituted-3-azabicyclo[3.1.0]hexanes (XI)

These compounds can be prepared from methyl acrylate and 2-benzylamino-3-[(tetrahydro-2H-pyran-2-yl)oxy]-propanoic acid methyl ester; heating these reagents in methanol provides an adduct which can be cyclized with sodium hexamethyldisilazide to 1-benzyl-4-oxo-5-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-pyrrolidine carboxylic acid methyl ester. Reduction and benzyl group removal is effected with Raney nickel; introduction of a benzyloxycarbonyl group is then followed by mesylation of the secondary alcohol and diazabicyclononane-mediated dehydration to give 1-benzyloxycarbonyl-2,5-dihydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-1H-pyrrole-3-carboxylic acid, methyl ester. Cyclopropanation with diiodomethane and zinc/silver couple, according to the method of Denis et al., Synthesis, 1972, 549, gives the bicyclo[3.1.0]-hexyl system of formula XI wherein the 1-substituent is CO_2CH_3, the 4-substituent is tetrahydropyranyloxy-methyl, and the 3-nitrogen is protected with benzyloxycarbonyl. The ester can be reduced to the corresponding alcohol wherein the 1-substituent is hydroxymethyl with lithium borohydride, or hydrolyzed with sodium hydroxide to the corresponding acid wherein

the 1-substituent is CO_2H. These two compounds can be manipulated as in Section VIII to provide the desired 1-substituent R^9; after protection of the 1-substituent, the 4-substituent R^3 can be generated from the tetrahydropyranyl-protected alcohol as in Section IX. Removal of the 3-benzyloxycarbonyl group can then be effected by hydrogenation.

1,6-R^6,R^7-Disubstituted-3-azabicyclo[3.1.0]hexanes (XII)

These compounds can be prepared from tert-butyl acrylate and N-benzylglycine methyl ester; 1-benzyloxycarbonyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid, tert-butyl ester is then synthesized *via* the methods described in Section XI. Molybdenum hexacarbonyl-mediated cyclopropanation with ethyl diazoacetate then provides the bicyclic system of the formula XII wherein the 1-substituent is t-butyloxycarbonyl, the 6-substituent is ethyloxycarbonyl, and the 3-nitrogen is substituted by benzyloxycarbonyl. Selective hydrolysis of the tert-butyl ester with trifluoroacetic acid can be followed by diborane-mediated reduction of the liberated carboxylic acid and protection of the derived primary alcohol as its tetrahydropyranyl ether. The 6-carboethoxy group can then be transformed into the desired 6-substituent as described above with respect to compounds of the formula XI; after protection of any primary or secondary amines, the tetrahydropyranyl group can be removed under acidic conditions and the primary alcohol can be elaborated into the desired 1-substituent by the methods outlined in Section VIII.

1,5-R^6,R^9-Disubstituted-3-azabicyclo[3.1.0]hexanes (XIII)

These compounds are derived from 1-benzyl-4-hydroxymethyl-3-pyrrolidine carbonitrile, whose

preparation is described by Achini and Oppolzer as mentioned in Section VII. Protection of the primary alcohol followed by nitrile hydrolysis and esterification provides 1-benzyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-pyrrolidine carboxylic acid methyl ester. The benzyl group can be removed by hydrogenation and replaced by a benzyloxycarbonyl group. Introduction of a thiophenyl group can then be effected via deprotonation with sodium hydride and reaction of the derived enolate with S-phenyl benzenethiosulfonate to give 1-benzyloxycarbonyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-thiophenyl-3-pyrrolidinecarboxylic acid methyl ester. Oxidation of the sulfur with hydrogen peroxide, followed by thermolysis of the derived sulfoxide then gives alkene 1-benzyloxycarbonyl-2,5-dihydro-4-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-pyrrolidinecarboxylic acid methyl ester. Cyclopropanation with diiodomethane provides the bicyclic system of formula XIII wherein the 1-substituent is methoxycarbonyl, the 5-substituent is tetrahydropyranyloxymethyl, and the 3-aza is substituted by benzyloxycarbonyl, which can be further elaborated as in Section XII to give all of the disubstituted compounds.

2,4-R^3,R^{10}-Disubstituted 3-azabicyclo[3.1.0]hexanes (XIV)

These compounds can be prepared from 3-benzyl-2-hydroxymethyl-3-azabicyclo[3.1.0]hexane by protection of the primary alcohol as the tetrahydropyranyl ether, debenzylation, introduction of a cyano group at the 4-position, and conversion into the desired 2- and 4-substituents according to the methods described in Section X.

3-Azabicyclo[4.1.0]heptane (XV)

Reaction of 1-benzyl-1,2,5,6-tetrahydropyridine with diazomethane and zinc iodide, according to the method of Attia, Ind. J. Chem., 16B, 98 (1978) provides 3-benzyl-3-azabicyclo[4.1.0]heptane. Hydrogenolytic removal of the benzyl group gives 3-azabicyclo-[4.1.0]heptane.

6-R^9-Substituted 3-Azabicyclo[4.1.0]heptanes (XVI)

Reaction of 3-benzylamino-1,2-dihydroxypropane with 4-bromobutanenitrile provides 4-[(benzyl) (2,3-dihydroxypropyl)amino]butanenitrile. Processing of this compound as in Section VII provides 3-benzyl-6-cyano-3-azabicyclo[4.1.0]heptane. The nitrile group of this compound can be transformed into the desired 6-R^9-substituents as described in Section VII.

5-R^5-Substituted-3-Azabicyclo[4.1.0]heptanes (XVII)

These compounds can be prepared from 3-azabicyclo-[4.1.0]heptan-4-one, disclosed in U.S. Patent 4,262,124. Reaction with sodium hydride and benzyl bromide provides 3-benzyl-3-azabicyclo[4.1.0]heptan-4-one, which can be subjected to treatment with strong base, such as lithium hexamethyldisilazide, and then reacted with formaldehyde. Subsequent protection of the resulting primary alcohol as the tetrahydropyranyl ether gives 3-benzyl-5-[(tetrahydro-2H-pyran-2-yl) oxy]methyl-3-azabicyclo[4.1.0]heptan-4-one. Lithium aluminum hydride reduction then yields the bicyclic system of the formula XVII where the 5-substituent is tetrahydropyranyl-protected hydroxymethyl. This substituent, after acid-induced removal of the THP group, can be transformed into the desired 5-R^5-substituent by utilizing the methods described in Section VIII.

4-R^3-Substituted-3-Azabicyclo[4.1.0]heptanes (XVIII)

These compounds can be prepared from

2-hydroxymethylpyridine by protection of the primary alcohol as the tetrahydropyranyl ether followed by reaction with benzyl iodide, and sodium borohydride reduction, according to the method reported by Sashida and Tsuchiya, Chem. Pharm. Bull., 32, 4600 (1984), to provide 1-benzyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]-methyl-1,2,3,6-tetrahydropyridine. Cyclopropanation with diazomethane/zinc iodide, according to the method of Attia in Section XV, then gives 3-benzyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-azabicyclo[4.1.0]-heptane. Acid induced removal of the tetrahydropyranyl group can be followed by methods described in Section VIII to provide the desired 4-R^3-substituent.

2-R^4-Substituted-3-Azabicyclo[4.1.0]heptanes (XIX)

Compounds of this type may be prepared from bicyclo[3.1.0]hexan-3-one by deprotonation with strong base, such as lithium hexamethyldisilazide, followed by quenching of the derived enolate with formaldehyde and protection of the resulting primary alcohol as the tetrahydropyranyl ether to provide 2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-bicyclo[3.1.0]hexan-3-one. Beckmann rearrangement of this compound, via the corresponding oxime tosylate, provides 2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-3-azabicyclo-[4.1.0]heptan-4-one. Reaction with benzyl bromide, followed by reduction with lithium aluminum hydride, then gives 3-benzyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]-methyl-3-azabicyclo[4.1.0]heptane; the protected hydroxymethyl 2-substituent can be transformed into the desired 2-substituent utilizing the methods described in Section IX.

1-R^6-Substituted-3-Azabicyclo[4.1.0]heptanes (XX)

Reaction of 3-(benzylamino)propanenitrile with 4-bromo-1,2-butanediol provides 3-[(benzyl)(3,4-

dihydroxybutyl)amino]propanenitrile. Processing of this compound as in Section VII gives 3-benzyl-1-cyano-3-azabicyclo[4.1.0]heptane. The nitrile group can be transformed into the desired 1-R^6-substituent as described in Section VII.

7-R^7-Substituted-3-Azabicyclo[4.1.0]heptanes (XXI)

These compounds can be prepared from 1-benzyl-5,6-dihydro-2(1H)-pyridinone by reaction with ethyl diazoacetate with molybdenum hexacarbonyl catalyst to provide 3-benzyl-2-oxo-3-azabicyclo[4.1.0]heptane-7-carboxylic acid ethyl ester, which can be reduced with lithium aluminum hydride to provide 3-benzyl-7-hydroxymethyl-3-azabicyclo[4.1.0]heptane. Utilization of the methods in Section VIII then yields the desired 7-R^7-substituent.

The pharmaceutically acceptable acid addition salts of compounds (I) are prepared in a conventional manner by treating a solution or suspension of the free base (I) with about one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration and recrystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, methanesulfonic, p-toluenesulfonic, cinnamic, fumaric, phosphonic, hydrochloric, hydrobromic, hydroiodic, sulfamic, and sulfonic acid.

The pharmaceutically acceptable cationic salts of compounds (I) may be prepared by conventional methods from the corresponding acids, e.g. by reaction with about one equimolar amount of a base. These cationic salts do not increase the toxicity of the compound toward animal organisms. Examples of suitable cationic salts are those of alkali metals such as sodium or

potassium, alkaline earth metals such as magnesium or calcium, and ammonium or organic amines such as diethanolamine or N-methylglucamine.

The novel compounds of formula I and the pharmaceutically acceptable acid addition salts thereof are useful in the treatment of bacterial infections of broad spectrum, particularly the treatment of gram-positive bacterial strains.

The compounds of the invention may be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally or in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25-500 ppm. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which can contain other solutes, for example, enough salt or glucose to make the solution isotonic. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1-50 mg/kg/day, advantageously 0.2-10 mg/kg/day given in a single daily dose or up to 3 divided doses.

The invention also provides pharmaceutical compositions comprising an antibacterially effective amount of a compound of the formula (I) together with a

pharmaceutically acceptable diluent or carrier.

The compounds of the invention can be administered to humans for the treatment of bacterial diseases by either the oral or parenteral routes, and may be administered orally at dosage levels of about 0.1 to 500 mg/kg/day, advantageously 0.5-50 mg/kg/day given in a single dose or up to 3 divided doses. For intramuscular or intravenous administration, dosage levels are about 0.1-200 mg/kg/day, advantageously 0.5-50 mg/kg/day. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art.

The antibacterial activity of the compounds of the invention is shown by testing according to the Steer's replicator technique which is a standard in vitro bacterial testing method described by E. Steers et al., Antibiotics and Chemotherapy, 9, 307 (1959).

The temperatures are in degrees Celsius in the following preparations and examples.

Preparation A

1. N-Benzyl-N-(2-cyanoethyl)-3-amino-1,2-propanediol

A solution of glycidol (25.4 ml, 0.383 mol) and 3-(benzylamino)propionitrile (50 ml, 0.319 mol) in ethanol (383 ml) was heated to reflux for 65 hours. Removal of solvent under reduced pressure left a yellow oil, which was partitioned between ethyl acetate and water. The organic layer was washed with water, washed with saturated sodium chloride solution and dried over sodium sulfate. Filtration and concentration in vacuo provided an oil (75 g) which was purified by column

chromatography (eluant: 5% methanol in chloroform) to give the title product (55.3 g, 0.236 mol, 74% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 3.86 (d, J=13 Hz, 1H), 3.8 (m, 2H), 3.64 (d, J=13 Hz, 1H), 3.53 (dd, J=13, 5 Hz, 1H), 3.20 (bs, 1H), 2.95 (m, 1H), 2.84 (m, 1H), 2.75 (dd, J=12, 8 Hz, 1H), 2.63 (dd, J=13, 4 Hz, 1H), 2.50 (m, 2H).

2. N-Benzyl-N-(2-cyanoethyl)-3-amino-1,2-bis(methanesulfonyloxy) propane

A solution of the title compound of Preparation A.1. (11.2 g, 47.8 mmol) and triethylamine (8.14 ml, 105 mmol) in methylene chloride (480 ml) was cooled to -10° and treated with methanesulfonyl chloride (16.6 ml, 119 mmol). After 85 minutes at -10°, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted twice with methylene chloride, and the combined organic layers were dried over magnesium sulfate. Filtration and removal of solvent in vacuo provided the title product as a yellow oil (18.0 g, 47.6 mmol, 99% yield) which was used without purification. ^{1}H NMR ($CDCl_3$): 7.31 (m, 5H), 4.75 (m, 1H), 4.45 (dd, J=12, 3, 1H), 4.27 (dd, J=12, 6 Hz, 1H), 3.68 (AB quartet, J=12 Hz, 2H), 3.07 (s, 3H), 3.02 (s, 3H), 2.88 (m, 4H), 2.48 (m, 2H).

3. 3-Benzyl-1-cyano-3-azabicyclo[3.1.0]hexane

N-Benzyl-N-(2-cyanoethyl)-2,3-dimethanesulfonylpropylamine (32.25 g, 85.2 mmol) was dissolved in benzene (800 ml), cooled to -10°, and treated with sodium hexamethyldisilazide (170 ml of a 1M solution in tetrahydrofuran, 170 mmol). After 2 hours, the reaction mixture was quenched with saturated ammonium chloride solution, and the mixture was extracted three times with methylene chloride. The combined organic

layers were dried over magnesium sulfat , filtered and concentrated in vacuo. Chromatographic purification (eluant: 4:1 hexane:ethyl acetat) gave the titl product as a yellow oil (8.23 g, 41.5 mmol, 49% yield). ^{1}H NMR ($CDCl_3$): 7.26 (m, 5H), 3.59 (s, 2H), 3.11 (d, J=9 Hz, 1H), 2.94 (d, J=9 Hz, 1H), 2.54 (d, J=9 Hz, 1H), 2.47 (dd, J=10, 4 Hz, 1H), 2.03 (m, 1H), 1.57 (m, 1H), 1.10 (dd, J=8, 5 Hz, 1H).

4. 1-Aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane

Lithium aluminum hydride (70 ml of a 1M solution in diethyl ether, 70 mmol) was added to a solution of 3-benzyl-1-cyano-3-azabicyclo[3.1.0]hexane (3.35 g, 16.9 mmol) in tetrahydrofuran (200 ml). After 18 hours at room temperature, the reaction mixture was treated sequentially with water (2.6 ml), sodium hydroxide (2.6 ml of a 15% aqueous solution), and water (7.8 ml). The mixture was filtered, and the filtrate was concentrated under reduced pressure to provide the title product as a viscous, slightly yellow oil (3.47 g, 100% yield), which was used without purification. ^{1}H NMR ($CDCl_3$): 7.20 (m, 5H), 3.54 (AB quartet, J=12 Hz, 2H), 2.92 (d, J=8 Hz, 1H), 2.87 (d, J=9 Hz, 1H), 2.81 (d, J=13 Hz, 1H), 2.59 (d, J=13 Hz, 1H), 2.33 (dd, J=8, 4 Hz, 1H), 2.25 (d, J=7 Hz, 1H), 1.10 (m, 1H), 0.97 (m, 1H), 0.30 (dd, J=8, 5 Hz, 1H).

5. 3-Benzyl-1-[(N-tert-butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hexane

A solution of the title compound of Preparation A.4. (2.19 g, 10.8 mmol) and triethylamine (1.8 ml, 13 mmol) in aqueous dioxane (8.8 ml water and 80 ml dioxane) was treated with di-tert-butyl dicarbonate (2.6 g, 11.9 mmol). After 1 hour at room temperature, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The

organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide a viscous, slightly yellow oil. Purification by column chromatography (eluant: 95:5:0.5 chloroform: methanol: concentrated ammonium hydroxide) provided the title product as a colorless oil (3.27 g, 10.8 mmol, 100% yield). ^{1}H NMR ($CDCl_3$): 7.26 (m, 5H), 4.54 (bs, 1H), 3.60 (AB quartet, J=13 Hz, 2H), 3.35 (m, 1H), 3.11 (dd, J=14, 6 Hz, 1H), 2.93 (m, 2H), 2.41 (dd, J=10, 4 Hz, 1H), 2.31 (d, J=8 Hz, 1H), 1.44 (s, 9H), 1.23 (m, 1H), 1.07 (m, 1H), 0.40 (dd, J=8, 4 Hz, 1H).

6. 1-[(N-tert-butoxycarbonyl)aminomethyl)]-3-azabicyclo[3.1.0]hexane

The title compound of Preparation A.5. (3.27 g, 10.8 mmol) and 10% palladium on carbon (3.44 g) were mixed with ethanol (500 ml), and the resulting suspension was treated with ammonium formate (2.04 g, 32.5 mmol) and heated to 60° for 7 minutes. The reaction mixture was cooled, filtered through diatomaceous earth (Celite (trademark)), and the solid cake was rinsed thoroughly with chloroform. Removal of solvent in vacuo provided a yellow-white residue, which was purified by column chromatography (eluant: 89:10:1 chloroform: methanol: concentrated ammonium hydroxide) to provide the title product as a white solid, mp 131.5-132.5° (1.53 g, 7.2 mmol, 67% yield). ^{1}H NMR ($CDCl_3$): 4.63 (bs, 1H), 3.31 (dd, J=12, 6 Hz, 1H), 3.24 (m, 1H), 2.88 (m, 4H), 1.40 (s, 9H), 1.23 (m, 1H), 0.54 (m, 1H), 0.42 (m, 1H).

Preparation B

1. 1-[(N-Acetyl)aminomethyl]-3-benzyl-3-azabicyclo-[3.1.0]hexane

A mixture of the title compound of Preparation A.4. (1.65 g, 8.16 mmol) and triethylamine (1.7 ml, 12 mmol) was treated with acetic anhydride (20 ml) and

allowed to stir at room temperature for 18 hours. The reaction solution was diluted with chloroform, washed with saturated aqueous sodium bicarbonate, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and filtered. Removal of solvent in vacuo provided the title product as a viscous yellow oil (1.97 g, 8.06 mmol, 99% yield). ^{1}H NMR ($CDCl_3$): 7.25 (m, 5H), 5.46 (bs, 1H), 3.61 (d, J=13 Hz, 1H), 3.51 (d, J=13 Hz, 1H), 3.48 (m, 1H), 3.16 (dd, J=14, 5Hz, 1H), 2.90 (d, J=9 Hz, 2H), 2.38 (dd, J=9, 3Hz, 1H), 2.25 (d, J=9 Hz, 1H), 1.94 (s, 3H), 1.22 (m, 1H), 1.05 (m, 1H), 0.39 (dd, J=8, 4Hz, 1H).

2. 1-[(N-Acetyl)aminomethyl]-3-azabicyclo[3.1.0]hexane

A solution of the title compound of Example B.1. (197.4 mg, 0.80 mmol) in ethanol (15 mol) was treated with palladium on carbon (10%, 254.4 mg, 0.24 mmol) and ammonium formate (151.3 mg, 2.4 mmol). The reaction mixture was allowed to stir at room temperature for 30 minutes, then was filtered through diatomaceous earth (Celite (trademark)). The colorless filtrate was concentrated in vacuo to provide the title product as a colorless semi-solid (149.4 mg, quantitative). ^{1}H NMR (CD_3OD): 3.42 (s, 2H), 3.25 (m, 4H), 2.00 (s, 3H), 1.6 (m, 1H), 0.84 (m, 1H), 0.71 (m, 1H).

Preparation C

1. 3-Benzyl-1-[N-(tert-butoxycarbonyl)ethylamino-methyl]-3-azabicyclo[3.1.0]hexane

The compound of Preparation A.4. (1.1 g, 5.4 mmol) was dissolved in methanol (55 ml) and treated with acetic acid (0.31 ml, 5.4 mmol), acetaldehyde (0.30 ml, 5.4 mmol) and sodium cyanoborohydride (341 mg, 5.4 mmol). The reaction mixture was allowed to stir at room temperature for 18 hours; it was then diluted with water and methylene chloride and acidified

to pH 1 with 6N hydrochloric acid. Potassium carbonate was then added until the pH of the aqueous layer was 10; the mixture was extracted three times with methylene chloride, and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was subjected to silica gel chromatography (eluant: 89:10:1 chloroform: methanol: concentrated ammonium hydroxide) to provide a colorless oil (390 mg, 2:1 mixture of 3-benzyl-1-ethylaminomethyl-3-azabicyclo[3.1.0]hexane and 1-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane). This material was dissolved in dioxane (18 ml) and water (2 ml) and treated with triethylamine (0.7 ml, 5.0 mmol) and di-tert-butyl dicarbonate (1.1 g, 5.0 mmol); the reaction mixture was allowed to stir for 18 hours at room temperature. The solution was partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The aqueous layer was extracted three times with methylene chloride and the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting colorless oil was subjected to purification on a Chromatotron (trademark) (eluant: 400:10:1 chloroform: methanol: concentrated ammonium hydroxide) to provide the title product as a yellow oil (277 mg, 0.84 mmol, 16% yield). ^{1}H NMR ($CDCl_3$): 7.30 (m, 5H), 3.65 (bs, 2H), 3.30 (m, 4H), 3.00 (m, 2H), 2.44 (m, 2H), 1.48 (s, 9H), 1.25 (m, 1H), 1.15 (m, 1H), 1.12 (t, J=7 Hz, 3H), 0.46 (bs, 1H).

2. 1-[N-(tert-Butoxycarbonyl)ethylaminomethyl]-3-azabicyclo[3.1.0]hexane

The title compound of Preparation C.1. (266.2 mg, 0.80 mmol) was dissolved in ethanol (8 ml), treated with ammonium formate (152 mg, 2.4 mmol) and 10% palladium on carbon (280 mg) and heated to 60° for 10

minutes. The reaction mixture was filtered through diatomaceous earth (Celite (trademark)) and the filtrate concentrated in vacuo; the residue was mixed with chloroform and filtered once more to provide, after removal of solvent, a colorless oil. This material was purified by silica gel chromatography (eluant: 95:5:0.5 chloroform: methanol: conc. ammonium hydroxide) to provide the title product as a colorless oil (45.6 mg, 0.19 mmol, 24% yield). ^{1}H NMR ($CDCl_3$): 3.43 (bs, 2H), 3.24 (bs, 2H), 2.90 (m, 3H), 2.46 (bs, 2H), 1.42 (s, 9H), 1.22 (bs, 1H), 1.08 (t, J=7 Hz, 3H), 0.55 (m, 1H), 0.46 (m, 1H).

Preparation D

1. 3-Benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylic acid

A mixture of 3-benzyl-1-cyano-3-azabicyclo-[3.1.0]hexane (2.77 g, 14.0 mmol) and barium hydroxide (4.47 g, 14.2 mmol) in water (100 ml) was heated to reflux for 18 hours. The reaction was then cooled and brought to neutral pH with sulfuric acid. The thick white mixture was filtered and washed twice with ethanol and twice with water. The filtrate was concentrated in vacuo, and the residue mixed with hot ethanol and filtered again. The filtrate was concentrated to provide the title product (2.91 g, 13.4 mmol, 96% yield). ^{1}H NMR (D_2O): 7.50 (bs, 5H), 4.36 (s, 2H), 3.9 (bs, 1H), 3.6 (m, 1H), 3.5 (bm, 2H), 2.14 (bs, 1H), 1.53 (bs, 1H), 1.09 (bs, 1H).

2. 3-Benzyl-1-isopropoxycarbonylamino-3-azabicyclo-[3.1.0]hexane

A mixture of the title compound of Preparation D.1. (4.72 g, 21.7 mmol), diphenylphosphoryl azide (4.68 ml, 21.7 mmol) and triethylamine (6 ml, 43 mmol) in isopropanol (210 ml) was heated to 80° for 18 hours. Volatiles were removed in vacuo and the residual oil

was dissolved in benzene. The benzene solution was washed with water, aqueous sodium bicarbonate, saturated sodium chloride and then dried over magnesium sulfate. Filtration and removal of solvent *in vacuo* gave a dark oil which was purified by silica gel chromatography (eluant: 289:10:1 chloroform: methanol: concentrated ammonium hydroxide) to provide the title product as a yellow solid, mp 88° (3.5 g, 12.8 mmol, 59% yield). ^{1}H NMR ($CDCl_3$): 7.26 (m, 5H), 4.92 (m, 2H), 3.60 (s, 2H), 3.03 (d, J=8 Hz, 1H), 2.87 (d, J=9 Hz, 1H), 2.61 (bs, 1H), 2.51 (d, J=8 Hz, 1H), 1.52 (bs, 1H), 1.32 (bs, 1H), 1.21 (d, J=6 Hz, 6H), 0.73 (dd, J=8, 4 Hz, 1H).

3. 1-Amino-3-benzyl-3-azabicyclo[3.1.0]hexane

The title compound of Preparation D.2. (1.43 g, 5.21 mmol) was treated with hydrochloric acid (7 ml of a 12 M solution) and heated to 100° for 18 hours. The reaction was then concentrated *in vacuo* to provide a viscous oil which was purified by silica gel chromatography (eluant: 189:10:1 then 89:10:1 then 85:14:1 chloroform: methanol: concentrated ammonium hydroxide). In this way the title product was obtained as an oil (661 mg, 3.51 mmol, 67% yield). ^{1}H NMR ($CDCl_3$): 7.27 (m, 5H), 3.60 (s, 2H), 3.02 (d, J=8 Hz, 1H), 2.84 (d, J=9 Hz, 1H), 2.50 (dd, J=8, 4 Hz, 1H), 2.33 (d, J=8 Hz, 1H), 1.9 (vbs, 2H), 1.18 (m, 1H), 1.09 (m, 1H), 0.63 (dd, J=8, 4 Hz, 1H).

4. 1-Acetylamino-3-benzyl-3-azabicyclo[3.1.0]hexane

Acetyl chloride (0.273 ml, 3.85 mmol) was added dropwise over 5 minutes to a solution of the title compound of Preparation D.3. (144.7 mg, 0.77 mmol), dimethylaminopyridine (47 mg, 0.38 mmol) and triethylamine (1.6 ml, 11.5 mmol) in tetrahydrofuran (10 ml). The reaction was allowed to stir at room

temperature for 18 hours; the solvent was then removed in vacuo and the residue diluted with methylene chloride. This organic solution was washed with aqueous sodium bicarbonate followed by saturated aqueous sodium chloride; after drying over magnesium sulfate, the solution was filtered and concentrated in vacuo to provide a dark red oil. Purification by column chromatography (eluant: 189:10:1 chloroform: methanol: concentrated ammonium hydroxide) provided the title product as a yellow oil (89.5 mg, 0.39 mmol, 51% yield). ^{1}H NMR ($CDCl_3$): 7.25 (m, 5H), 5.96 (bs, 1H), 3.60 (m, 2H), 3.07 (d, J=8 Hz, 1H), 2.87 (d, J=9 Hz, 1H), 2.63 (dd, J=9, 4 Hz, 1H)), 2.51 (d, J=8 Hz, 1H), 1.90 (s, 3H), 1.52 (m, 1H), 1.35 (m, 1H), 0.70 (dd, J=9 5 Hz, 1H).

5. 1-Acetylamino-3-azabicyclo[3.1.0]hexane

The title compound of Preparation D.4. (77.8 mg, 0.34 mmol) was dissolved in ethanol (20 ml) and treated with palladium on carbon (10%, 105 mg, 0.09 mmol); after addition of ammonium formate (78 mg, 1.24 mmol) the reaction mixture was heated to 60° for 1 hour. The reaction mixture was filtered through diatomaceous earth (Celite (trademark)), the diatomaceous earth washed well with ethanol, and the combined filtrates concentrated in vacuo to provide a yellow-green oil. Purification by silica gel chromatography (eluant: 1:1 chloroform: methanol with 1% ammonium hydroxide) provided the title product as a viscous oil (26.1 mg, 0.186 mmol, 55% yield). ^{1}H NMR (CD_3OD): 3.10 (m, 2H), 2.87 (d, J=11 Hz, 1H), 2.84 (d, J=11 Hz, 1H), 1.90 (s, 3H), 1.55 (m, 1H), 0.88 (d, J=7 Hz, 2H).

Preparation E

1. 5-Benzyl-1,3a,4,5,6,6a-hexahydro-4,6-dioxopyrrolo[3,4-c]pyrazole-3-carboxylic acid, ethyl ester

Ethyl diazoacetate (13 g, 114 mmol) in diethyl

ether (100 ml) was added dropwise to a solution of N-benzylmaleimide (10 g, 53 mmol) in diethyl ether (250 ml). The resulting mixture was allowed to stir for 18 hours; the solvent was then removed in vacuo, and the resulting residue partitioned between methylene chloride and water. The organic layer was dried over sodium sulfate, filtered and concentrated to provide the title product as a white solid, mp 145-146° with decomposition (16 g, 53 mmol, 100% yield). ^{1}H NMR ($CDCl_3$): 7.31 (m, 5H), 7.02 (bs, 1H), 4.89 (dd, J=11, 2 Hz, 1H), 4.65 (s, 2H), 4.55 (d, J=10 Hz, 1H), 4.36 (q, J=7 Hz, 2H), 1.37 (t, J=7 Hz, 3H).

2. [1α,5α,6α]-3-Benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione-6-carboxylic acid, ethyl ester

The title compound of Preparation E.1. (99 g, 0.33 mmol) was thermolyzed in a 185° oilbath; after 1.5 hours, the reaction was cooled to room temperature and the product recrystallized from diethyl ether to provide the title product as a white solid, mp 100-101° (31.2 g, 114 mmol, 35% yield). ^{1}H NMR ($CDCl_3$): 7.29 (s, 5H), 4.50 (s, 2H), 4.17 (q, J=7 Hz, 2H), 2.86 (d, J=3 Hz, 2H), 2.28 (t, J=3 Hz, 1H), 1.26 (t, J=7 Hz, 3H).

3. [1α,5α,6α]-3-Benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane

A solution of ethyl 3-benzyl-3-azabicyclo[3.1.0]-hexane-2,4-dione-6-carboxylate (2.73 g, 10 mmol) was added to a suspension of lithium aluminum hydride (1.5 g, 40 mmol) in tetrahydrofuran (250 ml). The resulting mixture was heated to reflux for 28 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride (2 ml) and filtered; the filtrate was concentrated in vacuo to provide the title product as a colorless oil (1.69 g, 8.3 mmol, 83% yield). ^{1}H NMR ($CDCl_3$): 7.27 (m, 5H), 3.58 (s, 2H), 3.43 (d, J=7 Hz,

2H), 2.96 (d, J=8 Hz, 2H), 2.35 (bd, J=9 Hz, 2H), 1.58 (m, 1H), 1.28 (s, 2H).

4. [1α,5α,6α]-3-Benzyl-3-azabicyclo[3.1.0]hexane-6-carboxaldehyde

Dimethylsulfoxide (0.48 ml, 6.8 mmol) was added to a -65° solution of oxalyl chloride (0.33 ml, 3.8 mmol) in methylene chloride (80 ml). A solution of the title compound of Preparation E.3. (0.75 g, 3.7 mmol) in methylene chloride (20 ml) was then added to the reaction mixture, still at -65°. After addition of triethylamine (2.0 ml, 16 mmol), the mixture was allowed to warm to room temperature. The solvent was then removed in vacuo, and the residue was partitioned between water and diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated to provide a light brown oil. Column chromatography (eluant: 20% ethyl acetate in hexanes) provided the title product as a light green oil (574 mg, 2.85 mmol, 77% yield). ^{1}H NMR ($CDCl_3$): 9.26 (d, J=5 Hz, 1H), 7.24 (m, 5H), 3.59 (s, 2H), 3.03 (d, J=9 Hz, 2H), 2.45 (bd, J=9 Hz, 2H), 2.40 (m, 1H), 2.06 (bs, 2H).

5. [1α,5α,6α]-3-Benzyl-3-azabicyclo[3.1.0]hexane-6-carboxaldehyde oxime

A solution of the title compound of Preparation E.4. (3.2 g, 16 mmol) in ethanol (160 ml) was treated with sodium acetate (4.25 g, 60 mmol) and hydroxylamine hydrochloride (3.2 g, 46 mmol) and allowed to stir for 18 hours. After removal of solvent in vacuo, the residue was partitioned between methylene chloride and aqueous potassium carbonate. The combined organic layers were dried over sodium sulfate and concentrated to provide the title product (3.29 g, 15.2 mmol, 95% yield). ^{1}H NMR ($CDCl_3$, mixture of geometrical isomers around oxime): 7.28 (m, 5H), 7.07 and 6.06 (d, J=8, 9

Hz, 1H), 3.61 and 3.60 (s, 2H), 3.07 and 3.04 (d, J=9 Hz, 2H), 2.75 and 2.10 (m, 1H), 2.41 (m, 2H), 1.64 (m, 2H).

6. [1α,5α,6α]-6-Aminomethyl-3-benzyl-3-azabicyclo-[3.1.0]hexane

The title compound of Preparation E.5. (3.2 g, 14 mmol) was dissolved in tetrahydrofuran (150 ml) and treated with lithium aluminum hydride (1.85 g, 49 mmol). The resulting suspension was heated to reflux for 12 hours. Water (5 ml) and a saturated solution of sodium potassium tartrate (2 ml) were added; the mixture was allowed to stir for 1 hour. Magnesium sulfate was added, and the mixture was filtered; removal of solvent from the filtrate provided the title product as a yellow oil (2.3 g, 11 mmol, 78% yield). ^{1}H NMR ($CDCl_3$): 7.27 (m, 5H), 3.58 (s, 2H), 2.96 (d, J=9 Hz, 2H), 2.50 (d, J=7 Hz, 2H), 2.34 (d, J=9 Hz, 2H), 1.38 (m, 1H), 1.32 (bs, 2H), 1.19 (bs, 2H).

7. [1α,5α,6α]-3-Benzyl-6-[tert-butoxycarbonyl)amino-methyl]-3-azabicyclo[3.1.0]hexane

The title compound of Preparation E.6. (150 mg, 0.74 mmol) was dissolved in dioxane (9 ml) and water (1 ml) and treated with triethylamine (0.15 ml, 1.1 mmol) and di-tert-butyl dicarbonate (165 mg, 0.76 mmol). The resulting solution was allowed to stir for 1.5 hours, and was then partitioned between diethyl ether and water. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to provide the title product as a pale green oil (216 mg, 0.71 mmol, 96% yield). ^{1}H NMR ($CDCl_3$): 7.27 (m, 5H), 4.73 (bs, 1H), 3.57 (s, 2H), 2.97 (m, 4H), 2.34 (bd, J=9 Hz, 2H), 1.44 (m, 10H), 1.25 (bs, 2H).

8. [1α,5α,6α]-6-(tert-Butoxycarbonyl)aminomethyl-3-azabicyclo[3.1.0]hexane

A mixture of the title compound of Preparation

E.7. (240 mg, 0.79 mmol), 10% palladium on carbon (240 mg) and ammonium formate (240 mg, 3.8 mmol) in ethanol (10 ml) was stirred at room temperature for 0.5 hour. The mixture was filtered and concentrated to give a gummy solid which was mixed with methylene chloride and filtered. Removal of solvents under reduced pressure gave a yellow oil which was crystallized from ethyl ether to give the title product as a white solid, mp 95-97° (148 mg, 0.70 mmol, 89% yield). ^{1}H NMR ($CDCl_3$): 8.47 (bs, 1H), 4.80 (bs, 1H), 3.33 (m, 4H), 3.06 (m, 2H), 1.66 (bs, 2H), 1.43 (s, 9H), 1.23 (bs, 1H).

Example F

1. [1α,5α,6α]-6-Hydroxymethyl-3-azabicyclo[3.1.0]-hexane

[1 ,5 ,6]-3-Benzyl-6-hydroxymethyl-3-azabicyclo-[3.1.0]hexane (2.5 g, 12 mmol) was dissolved in methanol (200 ml), treated with palladium hydroxide on carbon (20% palladium content, 500 mg) and stirred under 1 atmosphere of hydrogen for 4.5 hours. The reaction mixture was filtered, and concentrated in vacuo; the residue was mixed with acetonitrile and allowed to crystallize. Filtration provided the title product as an amorphous white solid, mp 98-100° (1.16 g, 10.2 mmol, 85% yield). ^{1}H NMR ($CDCl_3$): 3.49 (d, J=7 Hz, 2H), 2.98 (d, J=11 Hz, 2H), 2.85 (bd, J=12 Hz, 2H), 1.67 (bs, 2H), 1.33 (m, 2H), 0.89 (m, 1H).

2. [1α,5α,6α]-3-Benzyloxycarbonyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane

The title compound of Preparation F.1 (1.0 g, 8.8 mmol) was dissolved in dioxane (40 ml) and water (40 ml) and treated with sodium bicarbonate (3 g, 36 mmol) and benzyl chloroformate (1.3 ml, 9.1 mmol). After 30 minutes, the reaction mixture was extracted with ethyl acetate; the combined organic layers were dried over

sodium sulfate, filtered and concentrated to provide the title product as an oil (2.15 g., 8.7 mmol, 99% yield). ^{1}H NMR ($CDCl_3$): 7.32 (bs, 5H), 5.08 (s, 2H), 3.65 (m, 2H), 3.46 (m, 4H), 1.45 (m, 2H), 0.91 (m, 1H).

3. [1α,5α,6α]-3-Benzyloxycarbonyl-3-azabicyclo-[3.1.0]hexane-6-carboxylic acid

A solution of the title compound of Preparation F.2 (2.1 g, 8.5 mmol) in acetone (50 ml) was treated dropwise with Jones' reagent until an orange color persisted. Isopropanol was then added to quench excess oxidant, and the resulting mixture was partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate, filtered and concentrated to provide the title product as an oil (2.08 g, 8.0 mmol, 94% yield). ^{1}H NMR ($CDCl_3$): 7.32 (bs, 5H), 5.08 (s, 2H), 3.72 (m, 2H), 3.50 (bs, 2H), 2.13 (bs, 2H), 1.47 (t, J=3 Hz, 1H).

4. [1α,5α,6α]-3-Benzyloxycarbonyl-6-tert-butoxy-carbonylamino-3-azabicyclo[3.1.0]hexane

Diphenylphosphoryl azide (865 µl, 4 mmol), triethylamine (1.1 ml, 8 mmol) and the title compound of Preparation F.3. (1.0 g, 3.83 mmol) were dissolved in t-butanol (45 ml) and heated to reflux for 18 hours. The solvent was then removed in vacuo, and the residue partitioned between water and ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide a residue which was purified by column chromatography (eluant: 40% ethyl acetate in hexane). The title product was obtained as an oil (772 mg, 2.3 mmol, 60% yield). ^{1}H NMR ($CDCl_3$): 7.31 (s, 5H), 5.06 (s, 2H), 4.65 (bs, 1H), 3.70 (m, 2H), 3.46 (m, 2H), 2.26 (bs, 1H), 1.67 (bs, 2H), 1.41 (s, 9H).

5. [1α,5α,6α]-6-tert-Butoxycarbonylamino-3-azabicyclo[3.1.0]hexane

A solution of the title compound of Preparation F.4. (58 mg, 0.17 mmol) was treated with palladium on carbon (10% by weight, 60 mg) and ammonium formate (60 mg, 1 mmol) and heated to 65° for 15 minutes. The reaction mixture was then filtered through Super-cel and the filtrate concentrated in vacuo to provide the title product as a solid (28 mg, 0.14 mmol, 82% yield). ^{1}H NMR ($CDCl_3$): 4.65 (bs, 1H), 3.14 (d, J=12 Hz, 2H), 2.93 (m, 2H), 2.30 (bs, 1H), 1.59 (bs, 2H), 1.44 (s, 9H).

The following examples illustrate the invention.

Example 1

7-(3-Azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A solution of the hydrochloride salt of 3-azabicyclo[3.1.0]hexane (157 mg, 1.31 mmol), (prepared in a manner similar to that described in United States Patent 4,183,857) in dimethylsulfoxide (13 ml) was treated with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (348 mg, 1.31 mmol) and triethylamine (0.58 ml, 3.9 mmol) and heated for 18 hours. Filtration of the reaction mixture provided a white solid, which was purified by column chromatography (eluant: 1% acetic acid in chloroform, then 5% acetic acid in chloroform, then methanol) to give the title product as a white solid, melting point 290° (186 mg, 0.43 mmol, 33% yield). ^{1}H NMR (DMSO-d_6): 8.54 (s, 1H), 7.75 (d, J=14 Hz, 1H), 7.08 (d, J=9 Hz, 1H), 3.83 (dd, J=4, 10 Hz, 2H), 3.73 (bs, 1H), 3.62 (bd, J=10 Hz, 2H), 1.77 (m, 2H), 1.30 (d, J=6 Hz, 2H), 1.14 (bs, 2H), 0.77 (m, 1H), 0.30 (m, 1H).

Example 2

A. 7-{1-[N-tert-Butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hex-3-yl}-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-[(N-tert-butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hexane (0.30 g, 1.41 mmol) and triethylamine (0.39 ml, 2.8 mmol) in acetonitrile (20 ml) was treated with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (0.375 g, 1.41 mmol) and heated to 50° for 21 hours. The temperature was then increased to 80° for 24 hours. Filtration of the reaction mixture then provided the title product as a white solid, mp 235.5-236° (508 mg, 1.11 mmol, 79% yield). ^{1}H NMR ($CDCl_3/CD_3OD$): 8.62 (s, 1H), 7.84 (d, J=14 Hz, 1H), 6.88 (d, J=7 Hz, 1H), 5.06 (vbs, 1H), 3.84 (m, 2H), 3.68 (m, 1H), 3.58 (m, 1H), 3.48 (m, 1H), 3.36 (bs, 2H), 1.64 (m, 1H), 1.45 (s, 9H), 1.36 (m, 2H), 1.17 (m, 2H), 0.87 (m, 1H), 0.66 (m, 1H).

B. 7-(1-Aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, hydrochloride salt

The title compound of Example 2A (442.8 mg, 0.97 mmol) was mixed with hydrochloric acid (3.0 ml of a 6 M solution) and acetic acid (3.0 ml) and heated to 100° for 1 hour. The resulting solution was cooled and concentrated in vacuo by azeotropic distillation with toluene, to provide a yellow residue, which was triturated with isopropanol and filtered. The title product was obtained as a white solid, mp 250-261° with decomposition (350 mg, 0.89 mmol, 92% yield). ^{1}H NMR (DMSO-d_6): 8.57 (s, 1H), 7.79 (d, J=13 Hz, 1H), 7.11 (d, J=7 Hz, 1H), 4.00 (m, 1H), 3.81 (m, 1H), 3.71 (d, J=9 Hz, 2H), 3.70 (m, 1H), 3.18 (d, J=11 Hz, 1H), 3.06 (d, J=11 Hz, 1H), 1.88 (m, 1H), 1.38 (bd, J=7 Hz, 2H), 1.16 (bs, 2H), 1.06 (m, 1H), 0.68 (m, 1H).

Example 3

A. 7-{(1-[N-tert-Butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hex-3-yl}-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-[(N-tert-butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hexane (501 mg, 2.35 mmol) and triethylamine (0.655 ml, 4.7 mmol) in acetonitrile (25 ml) was treated with 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (668.3 mg, 2.35 mmol) and heated to 80° for 24 hours. Filtration of the reaction mixture then provided the title product as a white solid, mp 188-189.5° (851 mg, 1.79 mmol, 76% yield). ^{1}H NMR ($CDCl_3$): 14.6 (s, 1H), 8.72 (s, 1H), 7.80 (dd, J=13, 2 Hz, 1H), 4.67 (bs, 1H), 3.94 (m, 1H), 3.83 (d, J=10 Hz, 1H), 3.76 (s, 2H), 3.66 (d, J=10 Hz, 1H), 3.42 (dd, J=14, 6 Hz, 1H), 3.29 (bdd, J=14, 6 Hz, 1H), 1.44 (bs, 10H), 1.24 (m, 2H), 1.12 (m, 2H), 0.70 (m, 2H).

B. 7-[1-Aminomethyl-3-azabicyclo[3.1.0]hex-3-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, hydrochloride salt

The title compound of Example 3B (779.4 mg, 1.63 mmol) was mixed with hydrochloric acid (5.0 ml of a 6M solution) and acetic acid (5.0 ml) and heated to 100° for 1.75 hours. The resulting solution was cooled and concentrated *in vacuo* by azeotropic distillation with toluene, to provide a residue which was triturated with isopropanol and filtered. The title product was obtained as a light yellow solid, mp 251° with decomposition (556 mg, 1.35 mmol, 83% yield). ^{1}H NMR (DMSO-d_6): 8.63 (s, 1H), 7.74 (dd, J=13, 2 Hz, 1H), 4.08 (m, 1H), 3.90 (d, J=10 Hz, 1H), 3.70 (m, 3H), 3.17 (d, J=13 Hz, 1H), 3.03 (d, J=13 Hz, 1H), 1.73 (m, 1H), 1.15 (m, 4H), 0.93 (m, 1H), 0.66 (m, 1H).

Example 4

A. 7-(1-[(N-tert-Butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

A mixture of 1-[(N-tert-butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hexane (52.5 mg, 0.24 mmol) and triethylamine (66 µl, 0.48 mmol) in acetonitrile (3 ml) was treated with 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (70 mg, 0.24 mmol) and heated to 80° for 20 hours. Filtration of the reaction mixture then provided the title product as a white solid, mp 234° with decomposition (89.0 mg, 0.19 mmol, 79% yield). ^{1}H NMR ($CDCl_3$): 8.66 (s, 1H), 7.96 (d, J=12 Hz, 1H), 4.72 (bs, 1H), 4.11 (m, 2H), 3.80 (m, 2H), 3.58 (m, 1H), 3.36 (d, J=6 Hz, 2H), 1.60 (m, 1H), 1.43 (s, 9H), 1.22 (m, 2H), 1.02 (m, 2H), 0.88 (m, 1H), 0.58 (m, 1H).

B. 7-[1-Aminomethyl-3-azabicyclo[3.1.0]hex-3-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt

The title compound of Example 4A (89 mg, 0.194 mmol) was mixed with hydrochloric acid (1.5 ml of a 6M solution) and acetic acid (1.5 ml) and heated to 100° for 1 hour. The resulting solution was cooled and concentrated in vacuo by azeotropic distillation with toluene, to provide a residue which was triturated with isopropanol and filtered. The title product was obtained as a light yellow solid, mp 283° with decomposition (48.4 mg, 0.122 mmol, 64% yield). ^{1}H NMR (DMSO-d_6): 8.52 (s, 1H), 8.16 (bs, 1H), 7.95 (d, J=13 Hz, 1H), 4.18 (m, 1H), 4.02 (m, 1H), 3.86 (m, 2H), 3.66 (m, 1H), 3.08 (m, 2H), 1.86 (m, 1H), 1.24 (m, 2H), 1.06 (m, 3H), 0.61 (m, 1H).

Example 5

A. 7-(1-[(N-tert-Butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-[(N-tert-butoxycarbonyl)aminomethyl]-3-azabicyclo[3.1.0]hexane (209.6 mg, 0.99 mmol) and triethylamine (0.273 ml, 1.96 mmol) in dimethylsulfoxide (10 ml) was treated with 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (242.9 mg, 0.82 mmol) and heated to 80° for 42 hours. The reaction mixture was then concentrated in vacuo and the resulting solid was triturated with isopropanol to deliver the title product as a white solid, mp 212-213° with decomposition (183 mg, 0.376 mol, 46% yield). ^{1}H NMR ($CDCl_3$): 8.79 (s, 1H), 7.79 (d, J=13 Hz, 1H), 4.69 (m, 1H), 3.99 (m, 1H), 3.66 (m, 4H), 3.57 (s, 3H), 3.48 (m, 1H), 3.27 (m, 1H), 1.58 (bs, 1H), 1.46 (s, 9H), 1.19 (m, 2H), 0.98 (m, 2H), 0.72 (m, 2H).

B. 7-[1-Aminomethyl-3-azabicyclo[3.1.0]hex-3-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

The title compound of Example 5A (166.7 mg, 0.34 mmol) was mixed with hydrochloric acid (2.5 ml of a 6M solution) and acetic acid (2.5 ml) and heated to 100° for 3.5 hours. The resulting solution was cooled and concentrated in vacuo by azeotropic distillation with heptane, to provide a residue which was triturated with isopropanol and ether. The product was then dissolved in water (2 ml), brought to pH 8.5 with sodium hydroxide solution (0.1 N) and filtered to provide the title product as a greenish solid, mp 194-196° (36.6 mg, 0.095 mmol, 28% yield). ^{1}H NMR (D_2O/NaOD): 8.50 (s, 1H), 7.62 (d, J=14 Hz, 1H), 4.05 (bs, 1H), 3.71 (d, J=10 Hz, 1H), 3.55 (s, 3H), 3.5 (m, 3H), 2.90 (bd, J=13 Hz, 1H), 2.70 (bd, J=13 Hz, 1H), 1.44 (bs, 1H), 1.11 (m, 2H), 0.90 (bs, 2H), 0.62 (m, 2H).

Example 6

A. 7-(1-[(N-acetyl)aminomethyl]-3-azabicyclo[3.1.0]-hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

A mixture of 1-[(N-acetyl)aminomethyl]-3-azabicyclo[3.1.0]hexane (115.5 mg, 0.75 mmol) and triethylamine (312 µl, 2.25 mmol) in acetonitrile (20 ml) was treated with the ethyl ester of 7-chloro-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (283 mg, 0.74 mmol) and heated to 80° for 20 hours. Additional 1-(N-acetyl)-aminomethyl-3-azabicyclo[3.1.0]hexane (97 mg) was added portionwise over 2.5 hours until thin layer chromatography indicated the absence of starting naphthyridine. The reaction mixture was concentrated in vacuo, and the residue chromatographed on silica gel (eluant: 189:10:1) chloroform: methanol: concentrated ammonium hydroxide). The title product was obtained as a colorless oil (280.3 mg, 0.56 mmol, 76% yield). ^{1}H NMR ($CDCl_3$): 8.36 (s, 1H), 7.93 (d, J=13 Hz, 1H), 7.37 (bs, 1H), 7.07 (bs, 2H), 6.15 (bs, 1H), 4.36 (q, J=7 Hz, 2H), 3.48 (m, 6H), 2.02 (s, 3H), 1.50 (m, 1H), 1.37 (t, J=7 Hz, 3H), 0.81 (m, 1H), 0.43 (m, 1H).

B. 7-[1-Aminomethyl-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt

The title compound of Example 6A (231.2 mg, 0.46 mmol) was mixed with hydrochloric acid (3 ml of a 6M solution) and acetic acid (3 ml) and heated to 100° for 24 hours. The resulting solution was cooled and concentrated in vacuo to provide a residue which was mixed with isopropanol and isopropyl ether and filtered. The filtrate was concentrated, and the product triturated with a small quantity of cold

isopropanol to provide a white solid, which was dissolved in a minimum quantity of sodium hydroxide solution and acidified with hydrochloric acid until a precipitate appeared. Filtration provided the title product as a yellow solid, mp 201-203° (40 mg, 0.086 mmol, 19% yield). ^{1}H NMR (D_2O/NaOD): 8.25 (s, 1H), 7.80 (d, J=13 Hz, 1H), 7.45 (m, 1H), 7.15 (m, 2H), 3.5 (vbm, 4H), 2.70 (bd, J=13 Hz, 1H), 2.60 (bd, J=13 Hz, 1H), 1.39 (bs, 1H), 0.68 (bs, 1H), 0.20 (bs, 1H).

Example 7

A. 7-(1-[N-(tert-Butoxycarbonyl)ethylaminomethyl]-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-[N-(tert-butoxycarbonyl)ethylaminomethyl]-3-azabicyclo[3.1.0]hexane (45.3 mg, 0.18 mmol) and triethylamine (50 µl, 0.36 mmol) in acetonitrile (5 ml) was treated with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (50.0 mg, 0.18 mmol) and heated to 80° for 18 hours. Filtration of the reaction mixture provided the title product as a white solid (26.8 mg, 0.055 mmol, 31% yield). ^{1}H NMR ($CDCl_3$): 8.67 (s, 1H), 7.90 (d, J=15 Hz, 1H), 6.89 (d, J=7 Hz, 1H), 3.87 (bs, 2H), 3.5 (m, 5H), 3.3 (bs, 2H), 1.6 (m, 1H), 1.49 (s, 9H), 1.33 (m, 2H), 1.14 (m, 5H), 0.83 (m, 1H), 0.68 (m, 1H).

B. 7-(1-Ethylaminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, hydrochloride salt

The title compound of Example 7A (20.2 mg, 0.042 mmol) was mixed with hydrochloric acid (0.75 ml of a 6M solution) and acetic acid (0.75 ml) and heated to 100° for 2 hours. The resulting solution was concentrated *in vacuo* and the residue triturated with isopropanol and dried under vacuum to provide the title product as

a yellow solid, mp 289-293° with decomposition (11.2 mg, 0.027 mmol, 63% yield. ^{1}H NMR (DMSO-d_6, 107°): 8.6 (s, 1H), 7.85 (d, J=14 Hz, 1H), 7.2 (d, J=7 Hz, 1H), 4.05 (m, 1H), 3.75 (m, 4H), 3.3 (d, J=10 Hz, 1H), 3.2 (d, J=10 Hz, 1H), 2.9 (m, 2H), 1.95 (m, 1H), 1.45 (m, 2H), 1.3 (t, J=7 Hz, 3H), 1.2 (m, 3H), 0.75 (m, 1H).

Example 8

A. 7-(1-Acetylamino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

A mixture of 1-acetylamino-3-azabicyclo[3.1.0]-hexane (150 mg, 0.70 mmol) and triethylamine (0.48 ml, 3.5 mmol) in acetonitrile (7 ml) was treated with 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (192.1 mg, 0.68 mmol) and heated to 80° for 18 hours. Filtration of the reaction mixture provided the title product as a white solid, mp 275° with decomposition (135.8 mg, 0.35 mmol, 51% yield). ^{1}H NMR ($CDCl_3$): 8.55 (s, 1H), 8.49 (s, 1H), 7.96 (d, J=13 Hz, 1H), 4.22 (m, 1H), 3.98 (bs, 2H), 3.81 (m, 1H), 3.68 (m, 1H), 1.82 (bs, 4H), 1.12 (m, 5H), 0.78 (m, 1H).

B. 7-(1-Amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt

The title compound of Example 8A (133 mg, 0.34 mmol) was mixed with hydrochloric acid (2.5 ml of a 6M solution) and acetic acid (2.5 ml) and heated to 100° for 18 hours. The resulting solution was cooled and concentrated *in vacuo* by azeotropic distillation with heptane, to provide a residue which was triturated with isopropanol. The title product was obtained as a yellow solid, mp 230° with decomposition (114.7 mg, 0.30 mmol, 88% yield). ^{1}H NMR (DMSO-d_6): 8.57 (s, 1H),

8.01 (d, J=12 Hz, 1H), 4.35 (m, 1H), 4.00 (m, 3H), 3.66 (bs, 1H), 2.15 (bs, 1H), 1.40 (m, 1H), 1.18 (m, 2H), 1.09 (bs, 2H), 0.91 (bs, 1H).

Example 9

A. 7-(1-Acetylamino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

A mixture of 1-acetylamino-3-azabicyclo[3.1.0]-hexane (60 mg, 0.28 mmol) and triethylamine (195 µl, 1.4 mmol) in acetonitrile (10 ml) was treated with the ethyl ester of 7-chloro-6-fluoro-1-(2,4-difluoro-phenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (95.6 mg, 0.25 mmol) and heated to 80° for 20 hours. The reaction mixture was concentrated in vacuo, diluted with chloroform and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: 189:10:1 chloroform: methanol: conc. ammonium hydroxide) to yield the title product as a yellow oil (120.8 mg, 0.25 mmol, 100% yield). ^{1}H NMR ($CDCl_3$): 8.35 (s, 1H), 8.01 (d, J=13 Hz, 1H), 7.36 (m, 1H), 7.04 (m, 2H), 6.11 (bs, 1H), 4.35 (q, J=7 Hz, 2H), 3.96 (vbs, 1H), 3.69 (vbs, 3H), 1.96 (s, 3H), 1.73 (m, 1H), 1.37 (t, J=7 Hz, 3H), 1.06 (m, 1H), 0.71 (m, 1H).

B. 7-(1-Amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt

The title compound of Example 9A (116 mg, 0.24 mmol) was mixed with hydrochloric acid (3 ml of a 6M solution) and acetic acid (3 ml) and heated to 100° for 18 hours. The resulting solution was cooled and concentrated in vacuo to provide a residue which was

crystallized from ether/methanol. The resulting solid was dissolved in 0.5N sodium hydroxide solution and filtered. The filtrate was then acidified with hydrochloric acid until a precipitate appeared. Filtration of the resulting mixture provided the title product as a tan solid, mp 205° with decomposition (31.2 mg, 0.069 mmol, 29% yield). ^{1}H NMR (D_2O/NaOH)): 8.26 (s, 1H), 7.76 (d, J=13 Hz, 1H), 7.42 (m, 1H), 7.15 (m, 2H), 3.82 (vbs, 1H), 3.4 (vbm, 3H), 1.41 (bs, 1H), 0.86 (m, 1H), 0.29 (bs, 1H).

Example 10

A. 7-([1α,5α,6α]-6-[(N-tert-Butoxycarbonyl)aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

A solution of [1 ,5 ,6]-6-[(tert-butoxycarbonyl)-aminomethyl]-3-azabicyclo[3.1.0]hexane (75 mg, 0.35 mmol) in acetonitrile (10 ml) and triethylamine (2 ml) was treated with the ethyl ester of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (105 mg, 0.34 mmol) and heated to 80° for 18 hours. Removal of solvent *in vacuo* gave a residue which was subjected to column chromatography (eluant: chloroform, then 5% methanol in chloroform) to provide the title product (132 mg, 0.27 mmol, 79% yield). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.98 (d, J=13 Hz, 1H), 4.7 (bs, 1H), 4.35 (q, J=7 Hz, 2H), 4.08 (bd, J=11 Hz, 2H), 3.72 (bd, J=11 Hz, 2H), 3.45 (bs, 1H), 3.10 (m, 2H), 1.55 (bs, 2H), 1.40 (s, 9H), 1.36 (t, J=7 Hz, 3H), 1.15 (m, 2H), 0.98 (bs, 2H), 0.90 (bs, 1H).

B. 7-([1α,5α,6α]-6-Aminomethyl-3-azabicyclo[3.1.0]-hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt

The title compound of Example 10A (110 mg, 0.23

mmol) was dissolved in hydrochloric acid (6N, 6 ml) and acetic acid (6 ml) and heated to reflux for 18 hours. The solvents were then removed in vacuo, and the residue recrystallized from acetonitril-methanol. The title product was obtained as fine white needles, mp 272° with decomposition (27 mg, 0.068 mmol, 30% yield). ^{1}H NMR (D_2O, 93°): 9.5 (s, 1H), 8.6 (d, J=14 Hz, 1H), 5.0 (bd, J=10 Hz, 2H), 4.7 (bd, J=10 Hz, 2H), 4.5 (bs, 1H), 3.8 (d, J=6 Hz, 2H), 2.7 (bs, 2H), 2.1 (m, 2H), 1.8 (bs, 3H).

Example 11

A. 7-[1α,5α,6α]-6-tert-Butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

A solution of [1α,5α,6α]-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane (149 mg, 0.75 mmol) in acetonitrile (25 ml) and triethylamine (3 ml) was treated with the ethyl ester of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (230 mg, 0.74 mmol) and heated to 80° for 15 hours. Removal of solvent in vacuo gave a residue which was subjected to column chromatography (eluant:chloroform) to provide material which upon trituration with diethyl ether gave the title product (206 mg, 0.45 mmol, 60% yield). ^{1}H NMR ($CDCl_3$): 8.46 (s, 1H), 8.04 (d, J=13 Hz, 1H), 4.80 (bs, 1H), 4.37 (q, J=7 Hz, 2H), 4.17 (bd, J=11 Hz, 2H), 3.81 (bd, J=11 Hz, 2H), 3.46 (m, 1H), 2.38 (bs, 1H), 1.89 (bs, 2H), 1.45 (s, 9H), 1.39 (t, J=7 Hz, 3H), 1.18 (m, 2H), 0.99 (m, 2H).

B. 7-([1α,5α,6α]-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, dihydrochloride salt

The title compound of Example 11.A (170 mg, 0.37

mmol) was dissolved in hydrochloric acid (6N, 10ml) and heated t reflux for 24 hours. Th solvent was then removed in vacuo, and the residue recrystallized from acetonitrile-methanol. The title product was obtained as a pale yellow solid, mp 180° with decomposition (52 mg, 0.12 mmol, 34% yield). ^{1}H NMR (methanol-d_4): 8.65 (s, 1H), 7.93 (d, J=13 Hz, 1H), 4.3 (bm, 2H), 3.98 (bm, 2H), 3.72 (bs, 1H), 2.68 (bs, 1H), 2.26 (bs, 2H), 1.30 (bs, 2H), 1.12 (bs, 2H).

Example 12

A. 7-([1α,5α,6α]-6-tert-Butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

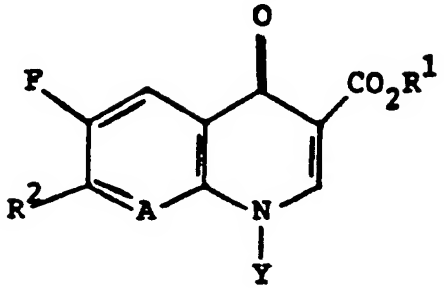
A solution of [1α,5α,6α]-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane (200 mg, 1.01 mmol) in acetonitrile (35 ml) and triethylamine (5 ml) was treated with the ethyl ester of 7-chloro-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (385 mg, 1.01 mmol) and heated to 90° for 18 hours. Removal of solvent in vacuo gave a residue which was partitioned between ethyl acetate and water. The organic layer was treated with activated charcoal, filtered, and concentrated; the residue was then subjected to column chromatography (eluant: 5% methanol in chloroform). The material thus obtained was recrystallized from diethyl ether to give the title product (296 mg, 0.54 mmol, 54% yield). ^{1}H NMR ($CDCl_3$): 8.35 (s, 1H), 8.06 (d, J=13 Hz, 1H), 7.37 (m, 1H), 7.05 (m, 2H), 4.72 (vbs, 1H), 4.37 (q, J=7 Hz, 2H), 3.81 (vbs, 2H), 3.55 (bm, 2H), 2.26 (bs, 1H), 1.78 (bs, 2H), 1.43 (s, 9H), 1.38 (t, J=7 Hz, 2H).

B. 7-([1α,5α,6α]-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt

The title compound of Example 12.A (250 mg, 0.46 mmol) was dissolved in hydrochloric acid (6N, 20ml) and heated to reflux for 24 hours. The solvent was then removed in vacuo, and the residue triturated with acetonitrile, washed with diethyl ether and recrystallized from acetonitrile-methanol. The title product was obtained as a pale yellow solid, mp 246° with decomposition (116 mg, 0.26 mmol, 57% yield). ^{1}H NMR (Methanol-d_4): 8.68 (s, 1H), 7.96 (d, J=13 Hz, 1H), 7.57 (m, 1H), 7.22 (m, 1H), 7.14 (m, 1H), 3.82 (vbs, 2H), 3.62 (vbs, 2H), 2.37 (bs, 1H), 2.03 (bs, 2H).

CLAIMS

1. A compound of th formula



...I

or a pharmaceutically acceptable acid addition salt thereof, wherein

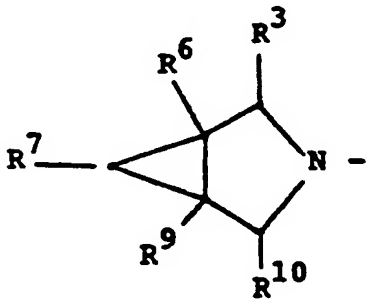
R^1 is hydrogen, a pharmaceutically acceptable cation, or (C_1-C_6) alkyl;

Y, when taken independently, is ethyl, t-butyl, vinyl, cyclopropyl, 2-fluoroethyl, p-fluorophenyl, or o,p-difluorophenyl;

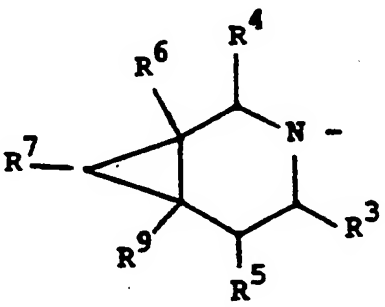
A is CH, CF, CCl, $COCH_3$, $C-CH_3$, C-CN or N; or

A is carbon and is taken together with Y and the carbon and nitrogen to which A and Y are attached to form a five or six membered ring which may contain oxygen or a double bond, and which may have attached thereto R^8 which is methyl or methylene; and

R^2 is selected from the group consisting of



and



wherein R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are each independently H, CH_3, CH_2NH_2, CH_2NHCH_3 or $CH_2NHC_2H_5$, and R^5, R^6, R^7 and R^9 may also independently be NH_2, $NHCH_3$ or NHC_2H_5, provided that not more than two of R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are other than hydrogen.

2. A compound according to claim 1 wherein R^1 is hydrogen.

3. A compound according to claim 1 wherein Y is cyclopropyl or o,p-difluorophenyl.

4. A compound according to claim 1, wherein said compound is

7-(3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-(1-ethylaminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

7-(1-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-(1-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

7-[(1α,5α,6α)-6-aminomethyl-3-azabicyclo[3.1.0]-hex-3-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

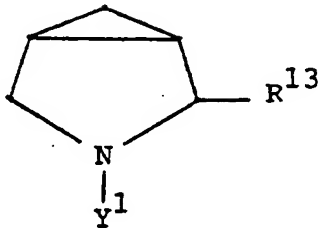
7-[(1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, and

7-[(1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

5. An antibacterial composition comprising an antibacterially effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

6. A method for the treatment of a bacterial infection which comprises administering to a subject affected by a bacterial infection an antibacterially effective amount of a compound according to claim 1.

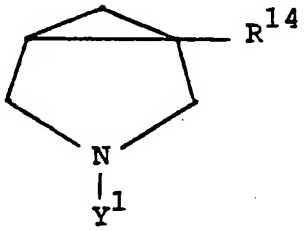
7. A compound of the formula



wherein Y^1 is hydrogen or benzyl, and R^{13} is methyl, cyano, hydroxymethyl, carboxyl or $CH_2NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl, or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

with the proviso that when Y^1 is hydrogen, then R^{13} is methyl or $CH_2NR^{11}R^{12}$ as defined above.

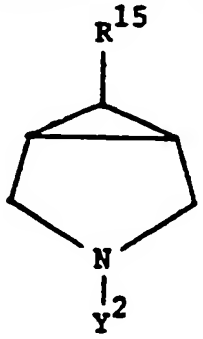
8. A compound of the formula



wherein Y^1 is hydrogen or benzyl, and

R^{14} is hydroxymethyl, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$, wherein R^{11} is hydrogen , methyl, or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

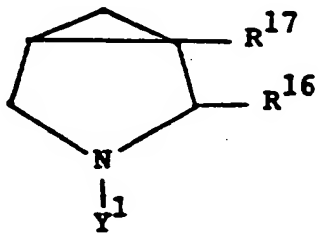
9. A compound of the formula



wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl, and

R^{15} is carboxyl, hydroxymethyl, CHO, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$ wherein R^{11} is hydrogen, methyl, or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

10. A compound of the formula

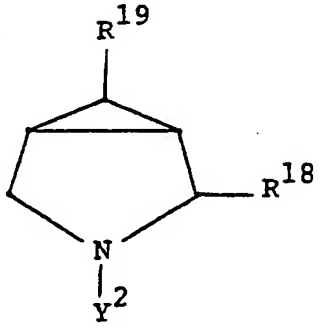


wherein Y^1 is hydrogen or benzyl,

R^{16} is methyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, or $CH_2NR^{11}R^{12}$, and

R^{17} is methyl, cyano, carboxyl, hydroxymethyl, or $CH_2NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

11. A compound of the formula

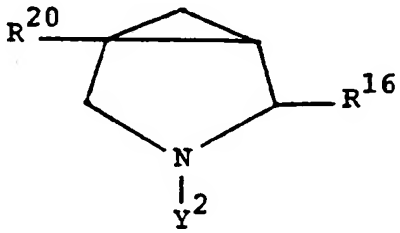


wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,

R^{18} is methyl, cyano, hydroxymethyl, or $CH_2NR^{11}R^{12}$, and

R^{19} is methyl, carboxyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

12. A compound of the formula



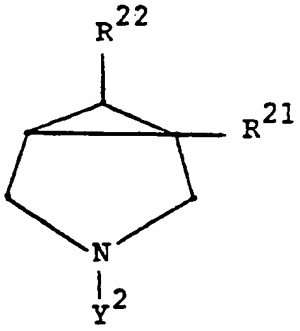
wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,

R^{16} is methyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, or $CH_2NR^{11}R^{12}$, and

R^{20} is methyl, carboxyl, hydroxymethyl, CHO, methoxycarbonyl, ethoxycarbonyl, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$ wherein R^{11} is hydrogen, methyl or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl,

trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

13. A compound of the formula

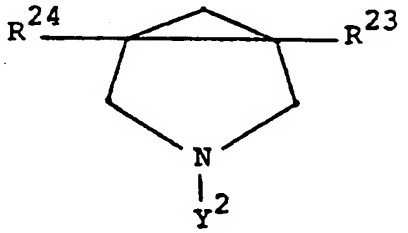


wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,

R^{21} is methyl, carboxyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, t-butoxycarbonyl, methoxycarbonyl, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$, and

R^{22} is methyl, carboxyl, hydroxymethyl, CHO, ethoxycarbonyl, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$ wherein R^{11} is hydrogen, methyl or ethyl and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

14. A compound of the formula



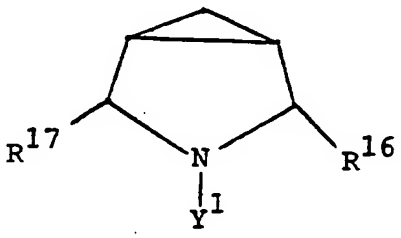
wherein Y^2 is hydrogen, benzyl, or benzyloxycarbonyl,

R^{23} is methyl, carboxyl, hydroxymethyl, CHO, methoxycarbonyl, $CH_2NR^{11}R^{12}$ or $NR^{11}R^{12}$, and

R^{24} is methyl, carboxyl, hydroxymethyl, CHO,

hydroxymethyl tetrahydropyranyl ether, $CH_2NR^{11}R^{12}$, or $NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

15. A compound of the formula



wherein Y^1 is hydrogen or benzyl,

R^{16} is methyl, hydroxymethyl, CHO, hydroxymethyl tetrahydropyranyl ether, or $CH_2NR^{11}R^{12}$, and

R^{17} is methyl, cyano, carboxyl, hydroxymethyl, CHO, or $CH_2NR^{11}R^{12}$, wherein R^{11} is hydrogen, methyl or ethyl, and R^{12} is hydrogen, C_1-C_6 acyl, C_2-C_6 alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, silyl, trityl, tetrahydropyranyl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphonyl, p-toluenesulfonyl, or benzyl.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/03489

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/44, 31/47, 31/535; C07D 217/26, 471/04, 498/06

U.S.Cl.: 514/230.2, 291, 294, 300, 312; 544/101; 546/84, 100, 123, 156

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/230.2, 291, 294, 300, 312; 544/101 546/84, 100, 123, 156

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	JP A, 64-56,673 DAINIPPON PHARMACEUTICAL, 3 March 1989. Note page 635 e.g. for Z is a 3-azabicyclo[3.1.0] hexan-3-yl group.	1-6
&	Japanese Patent Abstracts Section C, Section No. 606; Vol 13, No. 255 page 12, published 13 June 1989 by Japanese Patent Information Organization (Tokyo); Abstract No. 89-056673; (Abstract of Japanese Patent 64-056673).	1-6

[10] Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 NOVEMBER 1989	21 NOV 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Bernard Dentz BERNARD DENTZ

Form PCT/ISA/210 (second sheet) (Rev.11-87)

In the next 9 Groups ABH stands for the 1-azabicyclo [3.1.0] hexane group. Each of the Groups comprises intermediate compounds for the final product, anti-bacterial compounds of Group I.

II. Claim 7 drawn to 2-substituted ABH compounds.

III Claim 8 drawn to 1-substituted ABH compounds.

IV. Claim 9 drawn to 6-substituted ABH compounds

V Claim 10 drawn to 1,2-disubstituted ABH compounds

VI. Claim 11 drawn to 2,6-disubstituted ABH compounds.

VII. Claim 12 drawn to 2 5-disubstituted ABH compounds.

VIII, Claim 13 drawn to 1,6-disubstituted ABH compounds.

IX. Claim 14 drawn to 1 5-disubstituted ABH compounds.

X. Claim 15 drawn to 2 4-disubstituted ABH compounds.

The reasons for the holding of lack of unity of invention are as follows:

The intermediates may be used in the synthesis of other physiologically active compounds. That is they in all likelihood can have uses other than as intermediates for the Group I compounds.

Each intermediate compound group contains a vast number of widely differing compounds. The differing substitution pattern in each of the groups provides a practical way to denote individual inventions.